U. S. TREASURY DEPARTMENT
PUBLIC HEALTH SERVICE

DILAUDID
(DIHYDROMORPHINONE)

A Review of the Literature and a Study of Its Addiction Properties

SUPPLEMENT No. 113

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U. S. TREASURY DEPARTMENT
HENRY MORGENTHAU, JR., *Secretary*
U.S. PUBLIC HEALTH SERVICE
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DILAUDID (DIHYDROMORPHINONE): A REVIEW OF THE LITERATURE AND A STUDY OF ITS ADDICTIVE PROPERTIES

By M. R. KING, *Surgeon*, C. K. HIMMELSBACH, *Assistant Surgeon*, and B. S. SANDERS, *Psychologist*, *United States Public Health Service*

I. Survey of Experimental and Clinical Studies of Dilaudid

INTRODUCTION

A new drug which promises therapeutic values comparable to morphine, but free from the danger of habituation, attracts widespread attention. There has been no abatement in the search for a suitable substitute for morphine, in spite of numerous disappointments and failures.

The object of the present paper is to review the experimental and clinical findings concerning a recent morphine derivative, "dilaudid", claimed by some to be an ideal substitute for opiates, and to report the results of its use as a substitute for morphine in the treatment of addicts.

Dilaudid is the trade name applied to dihydromorphinone hydrochloride, ($C_{17}H_{19}O_3N \cdot HCl$), discovered by the A. G. Knoll chemical firm of Ludwigshafen, Germany. Its description in German patent literature appeared in 1923, but it was not until 1926 that experimental and clinical studies began to appear in German medical publications. According to Eddy (1933) a complete bibliography of dilaudid exceeds 200 titles. The bulk of this literature is to be found in German medical and technical journals.

CHEMICAL AND PHYSICAL PROPERTIES OF DILAUDID

The dilaudid, or dihydromorphinone, molecule differs from morphine in only two respects: (1) By the replacement of one of the hydroxyls by a ketonic oxygen, and (2) by the removal of an adjacent double bond by hydrogenation.

Dilaudid is obtained by the hydrogenation of morphine in a warm (60° to 90° C.) acid solution in the presence of a large excess of palladium, platinum, or their respective salts, used as a catalyst. It is a white crystalline powder containing 88.66 percent of the alkaloid base. It is readily soluble in water (1: 3) and in hot alcohol, but only sparingly soluble in cold alcohol and is insoluble in ether. When dissolved in water, dilaudid gives a neutral solution which,

when treated with ammonia or sodium carbonate, liberates the base, a white crystalline powder having a melting point of 259° to 260° C. The precipitate redissolves if mixed with caustic soda solution (Oehme, 1928).

Certain simple tests used in identifying dilaudid are as follows: A small amount of dilaudid, when dissolved in concentrated acid and heated gently after the addition of a drop of iron chloride, gives no color reaction, distinguishing it from morphine which, if treated similarly, gives a deep blue color (Schmitt, 1929).

Formaldehyde sulphate, when added to morphine solution, gives a striking reddish-violet color changing slowly to bluish violet; dilaudid solution, on the other hand, gives a yellow color first (Schmitt, 1929).

Dilaudid may be distinguished from morphine by the fact that it is soluble in ammonia. It may also be distinguished by means of crystallography, dilaudid crystals being widely different both in size and shape from morphine crystals. Dilaudid crystals from an alcoholic solution are very minute and rhomboid in shape. Microcrystalline tests are also valuable in distinguishing dilaudid from dicodid and eucodal (Steinmetz, 1928; King, 1931). With Wagner's reagent, dilaudid gives an amorphous precipitate, which distinguishes it from eucodal, the only opiate giving a crystalline precipitate with this reagent. The addition of Marquis' reagent gives characteristic color differences with dilaudid, dicodid, eucodal, and morphine, which can be easily identified when compared with identical treatments of known samples (King, 1931).

Adding iodic acid to sulphuric acid solution of dilaudid gives a more typical yellow tint than obtained from morphine. The addition of ammonia gives a mahogany color which, on standing, becomes distinctly reddish, while morphine treated similarly gradually assumes a dull brown color (King, 1931).

When to 1 mg of a dilute aqueous solution of a salt of dilaudid, morphine, dicodid, and eucodal, respectively, is added a 3 percent hydrogen peroxide and 7 percent ammonia solution followed by 1 drop of 10 percent copper sulphate solution, the following colors occur: Dilaudid, brown to yellow; morphine, brown to red; while eucodal and dicodid show no appreciable effect on the blue of the copper ammonia. On adding a few drops of 10 percent potassium cyanide, the colors given are as follows: Morphine, red; dilaudid, yellow; eucodal and dicodid, very pale red. The test may be made extremely delicate for dilaudid by reducing the amount of the reagent added. As little as $\frac{1}{20}$ mg can be detected with certainty, and the test distinguishes dilaudid from all other alkaloids (King, 1931).

The separation of dilaudid from a mixture of drugs is not difficult. The mixed bases should be extracted from an ammoniacal solution

by a mixture of chloroform and alcohol, and the extract evaporated to dryness. The extract should be dissolved in dilute hydrochloric acid and the solution made alkaline with sodium hydroxide. A chloroform extraction will now remove eucodal and dicodid, morphine and dilaudid remaining in the aqueous layer. This is saturated by ammonium sulphate and again extracted with chloroform, which removes dilaudid. Morphine may be removed from the aqueous layer by a mixture of alcohol and chloroform (King, 1931).

The specific rotations of the alkaloids may be utilized both in identifying them and in the determination of the amount present. If a narrow-bore polarimeter tube is used, an accurate determination may be obtained with as little as 100 mg (King, 1931).

A solution of dilaudid usually remains potent for 3 weeks or more. An exact period cannot be given, however, since the length of time depends on the type of bacteria present, the temperature, and the method of storing. If stored in an ordinary glass, the solution, after a time, becomes alkaline and discolored. A sterile solution, on the other hand, if stored properly, will keep its strength indefinitely (Schmitt, 1929).

PHARMACODYNAMIC PROPERTIES OF DILAUDID

While in general the pharmacodynamic effects of dilaudid are similar to those of morphine, there are certain characteristic variations which may be seen from a survey of literature dealing largely with animal experimentation.

Nau (1930) reported experiments on larvae of toads (*Bufo vulgaris*) and triton (*Triton vulgaris*) with different concentrations of dilaudid, morphine, and heroin, respectively. In each instance the larvae were kept in the solution until paralyzed. The time was noted when equilibrium was lost and when complete paralysis ensued. When the larvae were fully paralyzed, they were transferred to fresh water and the time of recovery, when recovery was possible, was noted.

The reaction of the larvae to the three drugs was essentially identical; with one conspicuous exception, no recovery followed the complete paralysis induced by morphine. In each instance with increased concentration beyond an effective limit, the time within which loss of equilibrium occurred, and also the time within which paralysis ensued, became shorter, and the time necessary for recovery (except in the case of morphine where no recovery occurred) was lengthened. Judging by the criterion of time necessary to produce complete paralysis, the following concentrations were found to be approximately equivalent: 1:50 (dilaudid)=1: 25 (morphine)=1:1,000 (heroin), or a ratio of toxicity of 1 : 0.5 : 20, respectively. Similar experiments on small fish resulted in a ratio of toxicity of 1 : 0.4 : 50, for dilaudid, morphine, and heroin, respectively. The comparative toxicity of

heroin was much greater in fish than in amphibia, while the comparative toxicity of morphine was approximately the same. In fish, death occurred in each instance following paralysis.

The comparative effects of the three drugs were also studied relative to their respective effects on the sartorius muscle of *Rana temporaria*. The muscle was subjected to different concentrations of dilaudid, morphine, and heroin and stimulated galvanically until it completely failed to react. It was then returned to Ringer's solution and the time noted for its recovery. The qualitative effect of the three drugs was the same.

Using the time necessary to induce paralysis as a criterion of effectiveness, there was an approximate toxicity ratio of 1 : 0.5 : 4 for dilaudid, morphine, and heroin, respectively. The comparative toxicity of dilaudid and morphine was the same, while that of heroin was approximately one-fifth the comparative toxicity on the larvae of the toad and triton. As in the former experiments, with greater concentrations the time necessary to induce paralysis was shortened, while the time of subsequent recovery was prolonged.

Nau (1930) further reported a series of comparative experiments with the hearts of 24 toads (*Bufo viridis*). Dilaudid in a concentration of 1 : 1,000 caused a decrease in amplitude with subsequent recovery and no change in frequency. A concentration of 1 : 800 caused a decrease in amplitude followed by partial recovery but no change in frequency. A concentration of 1 : 600 suppressed the amplitude by one-third and caused a slight decrease in frequency. A 1 : 500 concentration caused paralysis after 1 minute. In all instances the hearts completely recovered when rinsed with Ringer's solution. The results with different concentrations of morphine and heroin were qualitatively the same. The quantitative potency of dilaudid, morphine, and heroin necessary to affect the amplitude of the heart was 1 : 0.5 : 3 and for inducing paralysis 1 : 0.4 : 4, ratios which do not differ greatly from those observed in the experiments with muscle tissue. Nau's experiments indicate the general qualitative resemblance of the three drugs.

Gottlieb (1926) found that the injection of 0.5 to 1 mg of dilaudid produced cerebral narcosis in the frog followed by tetanic convulsions. Osman (1929) reported that the injection of 30 to 50 mg/kg (number of milligrams per kilogram of body weight) of a 2 percent dilaudid solution in the lympho-thoracic duct caused intense agitation without change in the reflexes or in spontaneous activity. A dose of 50 mg/kg produced slight hyperexcitability and diminution in spontaneity and in reflex action. A dose of 150 mg/kg caused intense agitation, in some instances within 2 or 3 minutes after the injection, with an increase in the respiratory rate. The agitation subsided after an hour or two, the animal then becoming calm and drowsy, with little spontaneity.

Some reflexes were disturbed while others still functioned normally. The quiet state lasted about an hour, after which the frog showed hyper-excitation when stimulated. The second stage of hyper-excitation lasted 2 to 3 hours, followed by exhaustion, calmness, and eventual recovery. With doses ranging from 50 to 150 mg/kg similar reactions were observed, except that the intensity was less with the smaller doses. Doses ranging from 180 to 200 mg/kg shortened or entirely abolished the initial period of excitation, the frogs being thrown into a state of complete exhaustion lasting 2 to 3 hours. The minimal fatal dose was rather variable, ranging between 200 and 300 mg/kg. It was noted that in summer the frogs were able to sustain higher doses than in winter. Osman appends the following comparative table:

Drug:	*Fatal dose mg/kg*
Morphine hydrochloride	1,000–1,500
Heroin	500
Eucodal	500
Dionin	300
Dilaudid	300
Codeine hydrochloride	200
Dicodid	130–160

Gottlieb (1926) concluded from experiments on rabbits that dilaudid was essentially like morphine, except that it was effective in doses one-third to one-fourth of those of morphine. Seven rabbits were used, 2 being treated with morphine, 3 with dicodid, and 2 with dilaudid. The main objective of the experiment was to secure the relative rates at which the respiration of rabbits would acquire tolerance to the 3 opiates. The initial effective dosage used was 0.3 mg/kg of dilaudid, 1 mg/kg of morphine, and 0.5 mg/kg of dicodid. The animals were injected every day, the dosages being kept constant, and the reaction on respiration was observed. After 4 weeks the respiratory retardation induced by morphine disappeared, indicating complete tolerance. On the other hand, the retardative effects of dilaudid and dicodid were essentially the same at the end of 7 weeks, showing no perceptible tolerance. In a second series of injections the findings for morphine were confirmed. The continuous administration of dicodid also showed a perceptible decrease in effectiveness; but no decrease was noted with dilaudid, even though the experiments were continued for 62 days. On the basis of these experiments Gottlieb concluded that the respiratory center of rabbits shows no tolerance to dilaudid.

The question of tolerance to morphine and dilaudid was more elaborately tested by Schoen (1929), who considered not only the effect on the respiratory center, but also the effect on postural and labyrinthine reflexes. In his experiments 20 rabbits were used. The

drugs were administered over variable periods of time and the effects noted. Qualitatively, dilaudid was shown to be similar to morphine. Schoen found definite evidence of acquired tolerance to dilaudid, but the rate at which tolerance was developed was much slower than with morphine. Injections given after a lapse of time to tolerant animals showed a loss of tolerance after 3 weeks in the case of morphine, while with dilaudid the tolerance was not completely lost. Other experiments showed that the removal of the cerebrum and the corpus striatum altered the effect of morphine and dilaudid on the respiratory center, causing an acceleration only. It also increased the tolerance so that the animal responded only to high doses. The removal of the midbrain and the frontal third of the pons caused a prolongation of the excitation period of the respiratory center. These experiments confirm the qualitative similarity of morphine and dilaudid. They suggest that, quantitatively, the excitatory effect of dilaudid is only twice that of morphine, while its paralyzing effects are five times as great.

Seeliger (1927) aimed to compare the effect of morphine and dilaudid on the retardation of peristalsis. Four rabbits were injected with morphine-scopolamine, dilaudid, and dilaudid-scopolamine, respectively. Through an abdominal window the retardation of peristalsis was noted as follows: Dilaudid, 6 hours; dilaudid-scopolamine, 7–8 hours; morphine, 14–16 hours; morphine-scopolamine, 16 hours.

Simenauer and Pulfer (1929) found that dilaudid, like morphine, increased the blood sugar content in rabbits.

Osman (1929) reported experiments with rabbits, using subcutaneous injections of solutions of dilaudid varying in concentration from 0.5 to 4 percent. The injections of 10 to 20 mg/kg caused somnolence for a short period, the animal regaining complete normalcy after 12 hours. In two cases the injection of 30 to 50 mg/kg produced somnolence lasting 4 hours. The animals were insensitive to pain and suffered from muscular weakness and at times abolition of corneal reflexes. Respiration was decreased to a rate of 15 per minute. When moving, the animals crept slowly. The effects prevailed for several hours, and complete recovery was attained after a lapse of 24 hours.

Injections of 100 mg/kg produced characteristic physiological changes after 2 minutes. Respiration became polypneac and the animal became somewhat restless. Five minutes later the animal was lying on its stomach, nose on the ground, and hind legs extended. Respiration dropped to about 20, becoming somewhat deeper and irregular with periodic cessations lasting approximately 10 seconds. Shortly after the injection the animal became gradually insensitive to sounds and pinching produced no effect other than the closing of the eye on the pinched side. However, even a slight pull on the

mustache or the eyelashes produced reflex reaction, and even protective movements. The nasal mucous membrane remained sensitive. The prostrate position, profuse salivation, and drooping ears completed the picture of intoxication. When the animal was awakened he would creep forward a little and fall asleep again. All the tendon reflexes were exaggerated, and at times muscular twitching of a convulsive character was noted. Eventually the animal revived from its torpor and made efforts to change its position; it advanced by crawling on its belly and became immobile once again. The somnolence, exaggerated tendon reflexes, and anesthesia prevailed for several hours. The animal recovered fully after 24 hours.

A dose of 150 mg/kg sometimes proved fatal. In one instance a state of somnolence was noted 5 minutes after the injection. There was a gradual insensibility to pinching of the ears, legs, skin, and belly. The corneal reflexes became progressively weak, while the patellar and other reflexes became exaggerated. Muscular twitching occurred now and then. The animal used for this experiment seemed to have recovered after 2 days, but it died on the following night. The autopsy showed renal congestion.

A dose of 200 mg/kg may result in death within 45 minutes. One animal lost its sensibility to pain 1 minute after the injection. The tactile sensitivity, however, was not abolished. Intense pinching of the ear caused a closing of the eye on the corresponding side. Three minutes after the injection the animal began to sink gradually, corneal reflexes were very weak, and respiration was reduced to 15 per minute. Ten minutes after the injection the tactile sense was still present. Fifteen minutes after the injection the animal became hyperexcited, and somewhat later facial convulsions were noted. Respiration was increased from 15 to 45 per minute. The animal would emerge from its torpor now and then, make a few movements, but soon reassume its prostrate position. Twenty minutes after the injection the shaking of the table on which the animal was laid induced exaggerated reflex action. The animal soon lost its orientation; hyperexcitation, torpor, and insensibility to pain prevailed. Somewhat later, generalized convulsions were noted, becoming more and more frequent. The animal was in a spasmodic state 25 minutes after the injection. About 5 minutes afterward, tetanic attacks with dyspnea followed, the animal was cyanosed and eventually succumbed in a violent attack.

By using successive small doses of dilaudid on rabbits at short intervals, Shoen observed the effects on respiration, circulation, and the internal organs. He noted that dilaudid inhibited the respiration very rapidly, lowering the rate from 12 to 14 per minute with some periodicity. The pulse was usually decreased in rate even though there seemed to be considerable variation in different animals.

The blood pressure first rose, but subsequently fell. The animal became somnolent and insensible to pain. It first showed hyperexcitation when stimulated, but later spontaneously with convulsions and spasmodic muscular twitching. The convulsions increased in severity and at times proved fatal. The respiration of the animal finally failed but could be revived by artificial respiration. Eventually the heart became seriously involved. Vasodilatation caused the blood pressure to drop and in some instances resulted in death of the animal. It is difficult to determine with precision a dose fatal for the respiratory center or for the heart, since animals vary from each other in this respect. When the respiratory center is revived artificially it is not affected by subsequent injections unless the dosage becomes very great or the injections are given too rapidly, in which case respiratory failure may again ensue and revival by artificial respiration may be impossible.

Autopsies on experimental animals which died within 2 to 3 days following a series of injections of dilaudid showed renal changes. One rabbit which died after 24 injections, 5 mg/kg (5-percent solution) administered over a period of 23 days, showed microscopic hemorrhages in the kidney, especially in Bowman's capsule. The canaliculi were dilated and contained many hyalin cylinders. There were very few leucocytes. In the uriniferous tubules there were some calcarious cylinders. The liver was markedly hyperaemic, and the capillaries were dilated. The follicles of the spleen were small and lacked germinative centers. Post-mortem examination of 3 rabbits and 9 guinea pigs which succumbed to dilaudid injections showed consistent lesions in the kidney and spleen as described above. Alterations found in the liver were not sufficiently consistent or specific to be attributed to dilaudid.

Osman compiled a table showing the comparative fatal dose of different opiates on the rabbit, as follows:

Drug:	*Fatal dose in mg/kg (hypodermic injection)*
Morphine hydrochloride	200–400–600
Dilaudid	200
Heroin	100
Eucodal	80–100
Dicodid	80
Codeine hydrochloride	50–100
Dionin	50–60

Weiss (1932) found that dilaudid had a morphine-like effect on the cornea of the rabbit and that it was as effective when one-fifth of the corresponding quantity of morphine was used. Eddy (1933) also noted the toxic similarity of dilaudid and morphine, the former being fatal in doses one-third of those of morphine. His experiments reconfirmed the observations on the depressive effect of dilaudid on

the respiratory center. According to Eddy the respiration was retarded as much by the use of 0.1 mg/kg of dilaudid as by 2 mg/kg of morphine, and that 0.1 mg/kg of heroin did not have the depressant effect equal to the same quantity of dilaudid. It was found that as little as 0.05 mg/kg of dilaudid was sufficient to affect the heart rate of the rabbit. Finally, contrary to the work of Seeliger and others, Eddy observed that the intestinal activity of the rabbit was suppressed by dilaudid in doses of one-fourth of the corresponding dosage of morphine.

Rady (1926), Seeliger (1927), and Haffner (1929) described experiments with guinea pigs showing the essentially morphine-like effect of dilaudid and that dilaudid is effective in much smaller doses. Osman (1929) has reported detailed experiments with a considerable number of guinea pigs. The observations on guinea pigs reconfirmed the general qualitative similarity of dilaudid to morphine as noted in rabbits. Post-mortem microscopic examinations also showed lesions in the kidney and spleen similar to the changes produced in rabbits. The following table compiled by Osman shows the fatal doses of different alkaloids for guinea pigs:

Drug:	*Fatal dose in mg/kg (hypodermic injections)*
Morphine hydrochloride	500
Dilaudid	200–250
Codeine hydrochloride	210
Heroin	200
Dionin	150
Eucodal	80–150
Dicodid	60

Rady (1926) described experiments with rats which show the qualitative similarity of dilaudid and morphine. The doses of dilaudid were one-half to one-third the correspondingly effective doses of morphine. The analgesic effects of dilaudid, morphine, and a large number of other drugs were tested by Haffner (1929), who found the minimum effective dose of dilaudid in mice and rats was 0.005 mg/kg and for morphine 0.0075 mg/kg; the two drugs produced like effects. Joel and Ettinger (1926) reported numerous experiments on rats injected with dilaudid, morphine, other opiates, hypnotics, and stimulants. The picture of acute poisoning from dilaudid was almost identical with that of morphine. A dose of 2 mg per 100 grams of body weight produced narcotic effects lasting from 2 to 4 hours, followed by a stage of excitation comparable with the effects produced by a dose of morphine 3 to 5 times greater. Experiments with animals habituated to morphine showed that these animals (six of them) were not narcotized by a 2 mg/100 g dose of dilaudid, but experienced merely the excitatory phase. The differential effect of dilaudid on morphine-habituated and nonhabituated rats indicated a

measure of cross tolerance between dilaudid and morphine. Eddy (1933) reported that the toxic effect of dilaudid in mice is quite identical with that of morphine. Both the narcotic and fatal doses of dilaudid were much less than the corresponding doses of morphine. According to Eddy, the toxicity of dilaudid in mice is six times greater than morphine.

The earliest detailed experimental work with dilaudid on cats is that of Oehme (1928). One animal was given a subcutaneous injection of 1 mg/kg of dilaudid. For about 20 minutes the cat drew itself up, made certain abnormal movements, and when called simply rubbed itself against its cage. No excitation was noted. When a dose of 2 mg/kg was administered, after a period the cat bent down on its fore part while the hind part kept its normal position more or less rigidly. This unusual pose was maintained for 1½ hours. No excitation or other symptoms were noted. A dose of 4 mg/kg precipitated a highly excited state after 25 minutes. The pupils were dilated to such an extent that the cat could not see, because of excessive light. There was also a measure of analgesia, the animal failing to respond when pricked by a needle. The excitation lasted for 9½ hours, but it began to subside after 5 hours. When one entered the cage, the cat would hiss, but would allow itself to be stroked. Following the period of excitation, the cat began rubbing itself against the cage, as in the two previous instances. A second cat was given a subcutaneous injection of 2 mg/kg. Five minutes afterward, severe vomiting resulted. The changes produced were otherwise similar to those observed in the first cat.

Schmitt (1929) concluded from his experiments on five cats that the effect of dilaudid was essentially the same as that of morphine. The injection of 1½ mg/kg produced excitation and dilation of the pupils. The cats ran up and down the cage attempting to escape, and when released from their cages they ran aimlessly around the room. The state of excitation terminated after 5 or 6 hours. After several days the same five cats were given a second subcutaneous injection of 2 mg/kg. The symptoms were very much the same as in the first instance. Vomiting did not occur. The cats were insensitive to pain. One aged cat showed shaking of the head, and 7 hours after the injection experienced clonic and tonic convulsions. This seemed to indicate that older cats are more susceptible to dilaudid.

Eddy's (1933) experiments confirm the qualitative similar effects of dilaudid, morphine, and heroin in minimum analgesic doses of 0.17 mg/kg, 0.75 mg/kg, and 0.52 mg/kg, respectively. Eddy found that the minimal analgesic dose of morphine precipitated excitation in the cat, while the minimal analgesic dose of dilaudid produced

no excitation. With regard to vomiting, Eddy states: "Cats have been seen to vomit with as little as 0.1 mg/kg of dilaudid and 0.5 mg/kg of morphine, while none of the animals which received heroin have vomited."

Gottlieb (1926) reported that, in regard to narcosis, analgesia, and inhibition of the respiratory rate in the dog, dilaudid produced morphine-like effects in doses one-third as large as morphine. A dose of 4 mg/kg was found sufficient to produce analgesia and narcosis.

Oehme (1928) presented detailed experiments with 13 healthy and 14 sickly dogs. The first healthy animal, 6 kg in weight and 16 months old, was injected with 2 mg of dilaudid 5 minutes after the animal had been fed with raw flesh. After 5 minutes the dog began to vomit profusely, and in another 10 minutes it became somnolent and insensitive to pain. The respiratory and pulse rates were decreased from 32 and 83 to 12 and 42, respectively. There was no change in temperature. Forty-five minutes after the injection, the abdominal muscles showed strong contractions. The dog defecated intermittently in small quantities. In the meantime it whined constantly, although the whining was barely audible. The animal made very few movements and after a time lay down on its right side. Soon thereafter convulsions were noted, reaching a maximum intensity about 75 minutes after the injection. After the convulsive period the pulse and respiration were not greatly changed. The dog went to sleep, though its whining continued. The animal awoke, with severe convulsions, 195 minutes after the injection. Three hundred and fifteen minutes after the injection the animal appeared normal and took food for the first time.

Observations on the remainder of the animals indicated certain similar reactions when the dose of dilaudid was sufficiently large to produce effects. The healthy animals usually vomited and became somnolent and analgesic, although in some cases the general sensorium seemed unaffected. Salivation and whining were usually noted. The respiration was decreased in most instances and in some was preceded by an initial increase. The pulse usually decreased and in some instances there was also a slight drop in temperature. In many instances dilaudid induced powerful contraction of the abdominal muscles. With doses of 2 mg/kg, the usual dosage, local and generalized convulsive seizures were observed in some of the animals. Doses of 2 mg and 4 mg were ineffective when administered orally. An oral dose of 20 mg produced general prostration and vomiting. A similar dose given subcutaneously induced groaning, excitation, dyspnea, heaving, and other serious disturbances, even though the animal responded to calls for a time after the injection. The animal was weak, and its reflexes eventually were absent. The pulse and

temperature were marked by depression. The respiration first increased greatly and then dropped. The animal finally suffered a complete collapse. In the diseased animals dilaudid usually induced sleep. Vomiting, salivation, and analgesia were noted in most cases. The effect on the respiratory system was rather variable, in some cases producing a decrease in the rate, in others an initial increase followed by a drop. The pulse likewise showed an initial increase in some instances even though a decrease in the rate was the more usual reaction. Temperature, whenever affected, declined. Cramps and convulsions were induced in a few cases. In summarizing his work, Oehme concluded that, in a given species, the size of animal is of little importance in gauging an affective dosage.

Another set of extensive experiments with dogs was reported by Schmitt (1929). Twenty-two healthy, well-fed animals were used. A short period (2 to 5 minutes) after the injection of 5 mg/kg, the animals became salivated and excited. After this initial period of excitation, defecation and powerful contraction of the abdominal muscles were noted. The gait of the animals was abnormal, indicating a lack of coordination, and there was evidence of fatigue. Out of a total of 50 injections, in only 3 instances was vomiting noted. In some cases the injection was given just after the animal had been fed, but this did not seem to change the results. Dilaudid caused a decrease in temperature, but the life of the animal was not otherwise endangered. The temperature remained low for about 6 hours, then began to increase, reaching normal after a period of 24 to 45 hours. It was noted that the smaller and younger animals recovered sooner than larger and older ones. In most of the cases defecation and flatulence occurred shortly after the injection. Unlike some animals in Oehme's series the anal reflexes were not affected. Intestinal sounds were frequent and loud. Sensitivity to pain was greatly decreased in all cases, reaching a maximum within 10 to 15 minutes after the injection. In most cases, however, the animals responded to needle pricks in the ear. Analgesia lasted from 4 to 5 hours. The injections did not induce true sleep but merely a sleep-like state, the eyes being open and the pupils dilated. When the surroundings were quiet, the dogs usually remained quiet. Some of the animals groaned, and the groaning was particularly strong at the end of narcosis. Noises frightened the dogs and precipitated efforts to escape. The animals were very uneasy and fearful; showing a hypersensitivity to auditory stimuli. The ears were usually erect following injection. The animals assumed most abnormal positions and many suffered from muscular twitching, usually localized in the hind legs. The action of the cerebrum was little affected, since well-trained dogs responded to calls and acted friendly. The recovery time varied rather widely in different animals, but in general it was much shorter in younger than in older animals.

Schmitt (1929), like Oehme, found that the duration of the effects of dilaudid was not prolonged by larger dosage, the period of recovery for the same animal being about the same with an injection of 5 mg/kg as with double that amount. Comparing his work with that of Frohner, who experimented with morphine, Schmitt points out the following differences: According to Frohner, younger dogs were more susceptible to morphine, while with dilaudid the opposite was the case. With morphine, sound sleep was produced by lethal doses, which is not true in the case of dilaudid; otherwise the qualitative effects of the two drugs were very much the same. According to Frohner 600 mg/kg of morphine was lethal in dogs, and the corresponding dosage for dilaudid was 500 mg/kg, indicating the relatively lesser toxicity of dilaudid. Schmitt (1929), in pointing out the advantages of dilaudid over morphine, emphasized the more rapid effectiveness of dilaudid and the fact that it seldom caused vomiting.

Eddy (1933) reports: "In dogs, vomiting has been seen after 0.05 mg/kg of dilaudid given subcutaneously, although our dogs have rarely vomited after 10 times that amount of morphine." Eddy, like other investigators, found dilaudid in doses as little as 0.05 mg/kg slowed the heart rate. In regard to intestinal activity, Eddy noted: "In dogs the same dose of each drug produced the typical modification of intestinal activity, particularly the increase in tone of the small intestine, characteristic of the action of morphine. Our experimental observations afford no explanation of the relatively weak constipating action of dilaudid reported clinically."

Krueger and Howe (1934) found that dilaudid has qualitatively the same effect as morphine on the intestinal musculature of a Thiry-Vella loop of the lower ileum (unanesthetized female dogs). The frequency of the segmenting was decreased while the amplitude was increased. Peristaltic waves developed and tone was increased. The minimal dose of dilaudid for producing a tone effect was about 0.01 mg/kg, while the corresponding dose of morphine was 0.1 mg/kg.

Detailed experiments with horses have been reported by Oehme (1928) only. Injections of 20 mg/kg and 40 mg/kg produced no significant physiological changes. Five minutes after an injection of 60 mg/kg of dilaudid a healthy horse made defensive movements and efforts to escape for no apparent reason. The tail was rigid and extended. Salivation was excessive. After 40 minutes, gradually increased excitation was noted, characterized by restlessness, stamping, and switching of the tail. Excitation attained its peak about 80 minutes after the injection, and a decline did not set in for nearly 3 hours. The animal became apprehensive, responding to all forms of external stimuli. Numbness became apparent 20 minutes after the injection, but during the course of observation superficial reflexes

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could be aroused by needle pricks. The physiological changes were as follows:

	Pulse	Respiration
Before the injection	36	20
15 minutes after the injection	30	16
40 minutes after the injection	30	12
60 minutes after the injection	34	10
150 minutes after the injection	38	12
420 minutes after the injection	43	21

Other observations on 12 diseased horses indicated, in general, the morphine-like effects of dilaudid. In small doses the respiration and pulse were usually decreased in rate and increased in amplitude. In larger doses, the usual reaction was first a lowered pulse and respiration and then a subsequent increase due to excitation. Still larger doses emphasized the excitatory effects. Drowsiness, quiet, and analgesia usually occurred with small doses. Larger doses tended to cause numbness in addition to excitation.

The only strictly experimental study of the effects of dilaudid on man is that of Rommelt (1927) on himself, dealing primarily with psycho-physiological changes. The experiment extended over a total of 29 days, divided into 3 periods—11 days in May, 9 days in June, and 9 days in September. During this period he took an injection of 3 mg of dilaudid on certain days, with intervening days on which 15 mg of dicodid were taken, or a physiologically neutral salt solution. A total of 8 dilaudid, 11 dicodid, and 10 salt solution injections were administered. The subject, suffering from exudative diathesis, was very sensitive to all forms of toxins. Shortly after the commencement of the experiment he was able to recognize the different injections by the sensations produced.

The effect of dilaudid was more immediate, brisk, intense, and prolonged in comparison with dicodid, the apparent effect of which disappeared after 8 or 10 minutes. The fatigue and apathy produced by dilaudid were perceptible even on the following morning. The injection produced a light, boring pain. Vasomotor reactions consisted of itching, especially of the finger tips, flushed skin, etc. There was a morphine-like effect on the activity of the intestines, but it did not lead to true constipation. A few minutes after the injection there was considerable nausea and vertigo. The limbs felt heavy, mental concentration became impossible, thinking was difficult, dream-like states prevailed, impressions became hazy, and memory was dulled. There was general apathy, loss of energy, fatigue, and a strong desire to sleep. A characteristic excitation and mild euphoria were also discernible. In the course of the experiment these secondary effects became more marked, especially so with dilaudid, causing physical exhaustion, followed by mild vertigo, persistent nausea, loss of appetite, and consequent loss of weight. Mentally the apparent stupor, lack of energy, and apathy were coupled with nervousness

and excessive irritability. Increased excitability in the sexual sphere was also experienced. According to the experimenters' own words, "In all instances there was a definite change in the state of consciousness not unlike that resulting from long habituation to morphine, but there was never a desire for the drug and no withdrawal effects. On the contrary, there grew up a strong antipathy against the continuation of injections."

The more subtle psycho-physiological effects of the drug were measured by comparative performance of certain simple psychophysical tasks: (a) Perception test; (b) typewriter test; (c) tests to determine threshold of sensation and pain; (d) choice reaction test; (e) ergographic test. Each morning the series of tests was repeated three times—first, before the injection; second, 10 minutes after the injection; and, third, after 15 minutes of rest. The results were compared, indicating unfavorable effects from the injections, particularly marked for dilaudid. The analysis of perception tests indicated sluggish, though incomplete and erroneous, impressions and lack of retentiveness. Emotional drives were also inhibited. Fatigue and sleepiness induced by the drugs were contributory factors in the decreased performance. The performance on typing test (typing of alphabet for 5 minutes) indicated an irritation of the lower motor centers and weakened volition. The number of errors was greatly increased. The choice reaction test indicated sluggishness and intellectual torpor. The test on the ergograph showed a decrease on normal days because of pain, while on drug days no such decline was noted, due to abolition of pain and possibly because of excitation of the motor centers. However, the performance was not improved, probably because of the slackening of the will.

In general, the qualitative effects of dilaudid and dicodid were alike, except that the effects of the former were more pronounced and more lasting. The experimenter, while under the influence of the drug, noted an inclination towards fantasy in the direction of an erotic feeling, but no typical euphoria. In considering the similarity of morphine and dilaudid, Rommelt observes that morphine experiments indicate no paralysis of intellectual functions; in fact some have claimed perceptible stimulation, which is not true for dilaudid. The experiment gave no indication of addiction, tolerance, or withdrawal symptoms. The experimenter, therefore, believes that even if addiction to dilaudid were possible, the danger must be much less than with morphine.

THERAPEUTIC PROPERTIES

The literature dealing with the clinical use of dilaudid is quite extensive, especially in Germany, where it was discovered and first used. A review of the various references pertaining to its therapeutic

properties shows that it has been given quite a thorough trial in the treatment of most disorders where morphine and other opiates are of value. Because of the amount and detail of much of the data, only the pertinent findings are included.

Zahler (1928) described the effects of therapeutic doses of dilaudid. He observed a slight decrease in pulse and respiration. There was also a slight initial increase in blood pressure, followed by a drop, not exceeding 10 mm. The skin first became flushed, but soon returned to normal. No constipation was noted. The daily use of the drug over a period of 3 months caused no discernible decrease in its therapeutic value. Zahler found that 5 mg by mouth was about as effective as 2 mg subcutaneously. He also noted that the addition of small amounts of phenacetin and antipyrine eliminated any slight narcotic effect that dilaudid may have, rendering it more universally useful for analgesic purposes.

Hoesselin (1930) observed the similarity between dilaudid and morphine on respiration, pulse, and blood pressure. He found no significant changes following the administration of 2 mg of dilaudid or 20 mg of morphine, either subcutaneously or intravenously, although the effects varied in different individuals. Intravenous injection of 4 mg of dilaudid, however, caused a drop of blood pressure from 130/65 to 120/60, a decrease in pulse rate from 70 to 66, and a decrease in respiration from 16 to 13 within 50 minutes. A similar dose of dilaudid, in a patient afflicted with delerium tremens, caused the blood pressure to drop from 120/70 to 96/60, the pulse to increase from 100 to 104, and the respiration to decrease from 24 to 12. A third case, a patient suffering from diabetic coma, was treated with 5 mg of dilaudid intravenously and showed a drop of blood pressure from 130/70 to 110/65, an increase in pulse rate from 110 to 122, and a decrease in respiration from 16 to 4 within 40 minutes. Other remedies had to be used in this case to prevent complete collapse.

Zahler (1930) reported that all opiates caused an initial increase in blood sugar. In fasting patients there was an increase from 10 to 25 percent following injections. The increase was greater for morphine than for dilaudid. Within 3 to 4 hours after the injections the blood sugar gradually dropped to a point below normal. Daily administration of morphine resulted in a gradual disappearance of this phenomenon after a period of 2 weeks. The blood sugar changes persisted for a period of 6 weeks when dilaudid was used. Prolonged usage of morphine finally lowered the blood-sugar content. An initial increase in the blood calcium was observed in most of his patients following injections of morphine and dilaudid. The increase was greater with morphine. The calcium content reached a maximum of 18 percent above normal after the daily use of morphine for 1 week. The maximum increase for dilaudid occurred after a period of 8 weeks and then

began to decline, even though daily administration of the drug was continued.

Dilaudid has been used by many clinicians in the treatment of respiratory diseases, especially pulmonary tuberculosis. Krehl (1926) usually administered one tablet (2.5 mg) each evening for the relief of cough in tuberculosis. In severe cases the dose was increased to four tablets during 24 hours. In all cases he observed marked relief from cough. One tablet of dilaudid appeared to produce greater and longer effects than 20 or 30 mg of codeine. He administered the drug both orally and subcutaneously. Kruskemper (1926) also concluded that dilaudid was superior to morphine or codein in relieving cough and inducing sleep in tuberculous patients. He found very few unfavorable reactions, and when they did occur they were relatively mild. Rady (1926) reported the results of treating 100 tuberculous patients with dilaudid. He also found that usually the hypodermic administration of 2 mg mitigated coughing and induced sleep without ill effects. Lowenthal (1927) found the administration of 2.5 mg of dilaudid as effective as 10 mg doses of morphine in the treatment of pulmonary hemorrhage complicating tuberculosis. Both Krehl and Rady considered the use of 5 mg doses of dilaudid very dangerous in the treatment of pneumonia, because of serious inhibition of respiration. On the other hand, Bescht (1927) obtained favorable results in pneumonia with doses of 2 mg. Very favorable results with dilaudid have been reported by Hemmerling (1926), Freundlich (1927) and others in relieving the symptoms of bronchiectasis, asthma, and other respiratory disorders. Giordano (1927) observed serious disturbance of respiration in a few cases when doses of 5 mg were used preceding operations. This disturbance did not occur when smaller doses were used. Trautman (1926) administered 5 mg of dilaudid to a patient afflicted with brain tumor, which resulted in repression of the respiration to a dangerous degree.

Grage (1927) reported the results of oral administration of dilaudid in a large number of tabetic patients, one or two tablets (2.5 mg) at each dose. In many patients there was a drop in blood pressure of 10 to 15 mm of mercury within 15 to 30 minutes. No albumen or other pathological changes were present in the urine or evidence of interference with liver function. Constipation was not noted. Slight euphoria was induced, different from that characteristic of morphine. Heinrich (1927) found dilaudid helpful in relieving psychic depression if one tablet (2.5 mg) was administered every 3 hours. However, the beneficial effects were of shorter duration than with morphine. Vidoni (1927–28) reported favorable effects on the central and vegetative nervous systems in relieving neuropsychiatric patients of their various symptoms. Richtzenhain (1930) relieved patients of mental depression by means of dilaudid administered over periods of 3 to 6

weeks without evidence of habituation or other ill effects. One of his patients, a narcomaniac, who was addicted to the use of morphine and other drugs, became addicted to dilaudid.

Dietrich (1926) used dilaudid, 2.5 mg, subcutaneously, one-half hour before operation on 42 cases. He found that less ether was required and that dilaudid produced a less constipating effect than morphine. Elleran (1926) reported similar results on a series of 300 operative cases. He concluded that dilaudid is superior to morphine in all respects for surgical work. He also found a mixture of scopolamine and dilaudid especially helpful in supporting anæsthesia. Dilaudid was also found more desirable than morphine for the relief of post-operative pain, because of its negligible by-effects. There was less vomiting, thirst, flatulence, and constipation. No ill effects or tendency toward habituation were noted in post-operative cases where dilaudid was used for prolonged periods, in one case for 40 days. Freundlich (1927) reported favorable results with the use of dilaudid in both pre-operative and post-operative care of gynecological cases. Lullies (1929) used dilaudid in more than 1,000 surgical and gynecological cases. As an analgesic it often proved superior to morphine. Undesirable effects were quite rare. Very few patients complained of nausea, and vomiting occurred in only 4 or 5 instances. He found 7.5 mg of dilaudid combined with 0.5 mg of atropine invariably effective in severe attacks of gallstone colic. Roedel (1930) emphasized the value of the intravenous administration of dilaudid. By this method he secured almost instantaneous relief from pain due to gallstones, renal colic, etc. Calmness and slight euphoria usually followed the injection. He found the intravenous method especially valuable in reducing fractures and dislocations. Schubert (1930) found dilaudid more effective in relieving severe attacks of renal and biliary colic when combined with atropine or papaverine. Lauger (1933) described his extensive experience with the use of dilaudid in genito-urinary work. He found it an excellent drug in all urological operative procedures.

Behlau (1927) reported 9 months' experience with dilaudid in eye, ear, nose, and throat work. He found the usual therapeutic dose (2.5 mg) of dilaudid to be slightly less effective for pain than 10 mg of morphine. He obtained the desired therapeutic effect, even in major operations, with 3 mg doses. He experienced less vomiting and vertigo with dilaudid and atropine than with morphine and atropine. Dilaudid-scopolamine given subcutaneously was also found superior to morphine-scopolamine. He did encounter patients, however, who were sensitive to dilaudid and could not tolerate it, even as some patients are sensitive to morphine. Similar favorable results were reported by Birkholz (1927) in the extensive use of dilaudid in otorhinolaryngology, especially in operative work.

In obstetrical cases, Freundlich (1927) observed no injurious effects on the mother or infant when dilaudid was used. The drug was found to be about 10 times more effective than morphine and very helpful in mitigating labor pains without interruption of labor. Sachs (1927) used dilaudid in obstetrical cases without affecting the heart of the infant or interrupting labor. He used doses of 2 mg, repeated after 6 hours when necessary. By using dilaudid he found it unnecessary to induce "twilight sleep." Schaefer (1930) found that the use of 3 mg of dilaudid subcutaneously or 5 mg suppositories preserved and even enhanced the natural pauses of labor without interruption of the usual course. He warned against using the drug at the inception of labor or at the time of expulsion and against repetition of the dose at short intervals. Altner (1931) reported the use of dilaudid in 150 deliveries. Doses of 5 mg administered in the form of suppositories were found excessive, as profound sleep was induced and labor was interrupted. He obtained good results by using one dose in the form of 2.5 mg suppository in 96 percent of his cases. He also cautioned against the use of the drug at the time of inception of labor or at the time of expulsion of the fetus. With proper doses he observed no ill effects on the mother or the infant.

Basch (1926) found dilaudid five times more effective than morphine and almost free from undesirable side-effects when used as an analgesic in gall-stone colic, renal calculus, and other painful disorders. As an analgesic and sedative it proved equally valuable in circulatory diseases, especially in relieving the pain incident to coronary sclerosis and disease of the aorta. Fuerst (1926) used dilaudid in a variety of painful disorders such as cancer, arthritis, epididymitis, X-ray burns, iritis, etc. One patient with an X-ray burn was receiving doses of 10 to 20 mg of morphine, which finally became ineffective. Dilaudid was substituted during the last 4 months of treatment, first with doses of 5 mg which were gradually increased to 10 mg. Before dismissal, the drug was gradually decreased and finally discontinued without withdrawal symptoms. Following 1 year's experience with dilaudid, Hemmerling (1926) felt that it may be used advantageously in all instances where analgesia is desired, especially in disorders of the circulation. As an analgesic, Kruskemper (1926) found 5 mg of dilaudid equivalent to 20 mg of morphine. The relief of pain was noted within 10 or 15 minutes after the injection and continued for 10 hours or longer. He concluded that dilaudid is indicated on all occasions when morphine is required, especially if prompt relief is desired, where large doses are necessary, or when morphine has already been used for some time. Alvarez (1932) found dilaudid five times stronger than morphine, free from constipating effects, and with little, if any, euphoric effects. He found it free from by-effects except nausea. He diminished the nauseating effects in one patient

by administering barbital with dilaudid. Leyton (1932) concluded from his experience with dilaudid that transient nausea, giddiness, and confusion may occur following administration, that the dose does not have to be increased, that it is not constipating, that the appetite is not impaired, and that euphoria occurs in but few cases.

Many other physicians, Von Werthern (1926), Bescht (1927), Boebncke (1927), Giordano (1927), Hartung (1927), Hilger (1927), Sterchel (1927), Schlueter (1927), Schneider (1928), Bender (1929), Chron (1929), Markowicz (1929), Paeprer (1929), Simenauer and Pulfer (1929), Schultz (1930), and others have described their experiences with dilaudid with special reference to the value of the drug in the treatment of painful disorders. In general, their results agree with the findings previously described. There appears to be universal agreement that dilaudid is a powerful analgesic and that the effect is produced quickly. Most of the authors feel that the beneficial effects are of longer duration than with morphine. Compared with morphine it is about five times stronger. The favorite mode of administration has been subcutaneous injections in surgical cases, by mouth in respiratory disorders, and in the form of suppositories in obstetric work. However, there has been considerable variation in the choice of the method of administration by various physicians. Most of the reports emphasize the freedom from undesirable by-effects commonly produced by morphine and the lack of danger of acquiring addiction. The value of dilaudid as a powerful agent in relieving cough, dyspnea, and respiratory discomfort in pulmonary disorders is stressed in many reports. The lack of constipating effects is also emphasized. The danger of inhibition of respiration is mentioned in connection with the use of large doses. However, several instances are recorded where very large doses have been used in exceedingly painful conditions without detrimental respiratory effects. Dilaudid in combinations with scopolamine has been successfully used as a powerful sedative. Combined with atropine it has been shown to be an effective antispasmodic in conditions where pain is a factor.

The degree of euphoria, if any, appears to be almost negligible, according to most of the reports. A few authors report slight euphoria, different from that of morphine. However, as reported by Alvarez (1932), "The great difficulty in estimating the amount of euphoria produced in man comes from the fact that individuals vary so much in their responses to drugs. Some so dislike the unpleasant by-effects of morphine that it would be almost impossible for them to develop a craving for it, whereas others experience such delightful sensations that they soon return begging for another dose." Addiction to the use of dilaudid following its administration over periods of time of several months appeared to be practically nil. Most of the authors who had extensive experience with the drug observed no evidence o

addiction and found no difficulty in decreasing the dose or withdrawing it entirely when indicated. Some of them were unwilling to deny the possibility of addiction to dilaudid and cautioned against it. A few observed definite evidence of addiction. Grage (1927) found dilaudid addicting but less dangerous than morphine. Martin (1927–28) cited one case of dilaudid addiction in a woman in whom treatment to break the habit was unsuccessful. Martin believed, nevertheless, that the danger of addiction to dilaudid was much less than to morphine. Wolff (1928–32) forwarded 394 questionnaires dealing with the prevalence of drug addiction to various medical institutions throughout Germany. He received 211 answers and discovered 8 cases of dilaudid addiction. He concluded that dilaudid is not free from addictive properties and should be included under the opium law. This has been done.

With dilaudid, Grage (1927) was successful in mitigating the withdrawal symptoms of morphine. He does not consider dilaudid free from addictive properties, but considers it much less dangerous than morphine. Hoesselin (1930) noted that usually when habituation to morphine was great, dilaudid was correspondingly less effective. For instance, a patient accustomed to 100 mg doses of morphine required 6 mg of dilaudid. Heinrich (1927) relieved the withdrawal symptoms of three morphine addicts with the use of dilaudid and believed the euphoria induced was basically different from that characteristic of morphine. Taschenberg (1926) observed no withdrawal symptoms in neuralgic patients who were given dilaudid over long periods of time. He questioned patients who had used both morphine and dilaudid as to the psychic effects of the latter. He found no definite euphoria. Klemperer (1929) reported experimental and clinical work with special reference to the addictive possibilities of dilaudid. A total of 10,000 tablets (2.5 mg) were administered by mouth, mostly to tuberculous patients; 2,000 suppositories (5 mg), mostly in surgical cases; and, 300 injections (2, 4, and 6 mg). From 1 to 6 tablets usually were ample for the tuberculous patients. Doses were increased only in a few instances and untoward effects were mild and rare. Subcutaneous injections of 2, 4, and 6 mg for analgesic and euphoric purposes frequently produced numbness and undesirable by-effects. The sedative and narcotic effects were inferior to morphine. Suppositories of 5 mg were found to be the most satisfactory. In some cases one suppository sufficed to abolish pain for many hours and induce restful sleep. No ill effects or evidences of habituation were observed.

A report by the Committee of Experts on Heroin, appointed by the League of Nations (1931), states: "For the relief of pain in patients in whom it is undesirable to act on the bowels, heroin is better than morphine, but dilaudid offers the same advantages. This alkaloid

has the same type of effect on the respiratory center as heroin, but is weaker; it has about the same influence as heroin in its pain-relieving properties, and, like heroin, has but little effect on the alimentary canal. Furthermore, the euphoric effects of dilaudid are weaker than those of both morphine and heroin as gaged by withdrawal symptoms."

II. A Study of the Addiction Liability of Dilaudid

METHODS

The method employed in this investigation is based on the ability of the substance in question completely and satisfactorily to replace morphine in addicts. A nonaddictive substitute should prevent the appearance of abstinence phenomena during the period of transition and substitution. It should not maintain the "addicted state" of the individual, and when withdrawn several days later, no evidence of abstinence should result. An addictive substitute, however, should not only prevent the appearance of abstinence during the period of substitution, but should support and maintain the "addicted state" so that after withdrawal the usual syndrome which follows abrupt morphine deprivation should occur. A substance which will support and maintain the "addicted state" is essentially addictive in itself.

For the purpose of this investigation seven volunteer morphine addicts were accepted as study subjects. These men were all confirmed addicts with strong and valid habits on admission, but otherwise essentially normal. Their habits were supported by the administration of four daily hypodermic doses of morphine sulphate for a few days after admission until they had become physically and psychically "stable". Effective doses of dilaudid were then substituted for each dose of morphine and stability was maintained by the substituted product for 12 to 17 days. The subjects were not informed of the substitution until 1 week after the change had been made. Withdrawal was abrupt and complete and few or no routine therapeutic measures were administered during the acute severity of abstinence.

Throughout the entire period of investigation the subjects were completely isolated from the remainder of the inmates of the institution. Observation and supervision were maintained 24 hours daily so that absolute uniformity and control of all conditions were assured. The subjects were weighed, stripped, each morning before breakfast. All other physical determinations were made after 5 minutes' rest in bed. Blood pressure determinations were made each morning before breakfast. Observations, injections, and meals had the same daily time relationships throughout the entire period. Sleep was recorded as the total amount observed during 24-hour periods. The defecation values reported are mostly subjects' statements. Each subject took a uniform dose of 1 ounce of mineral oil and cascara

mixture *per os* each night at 9 p. m. Observations for specific signs of abstinence were made three times daily. These included the presence (and degree) or absence of certain characteristic signs pertinent to the abstinence syndrome as follows:

MILD	MARKED
Yawning	Air hunger
Lacrimination	Restlessness
Rhinorrhea	Insomnia
Perspiration	Elevation of blood pressure
MODERATE	
Goose flesh	SEVERE
Dilation of pupils	Emesis
Muscle tremor	Diarrhea
Anorexia	Weight loss (5 lbs. or more)

RESULTS

The complete data on the seven subjects are presented in tabular form in tables 1 to 7, depicting the condition of each subject in terms of abstinence throughout the entire period of investigation. The data indicate that dilaudid will promptly and completely substitute for morphine without permitting the appearance of abstinence phenomena, showing that complete cross-tolerance exists between these substances. Except in case no. 7, none was aware of the substitution during the first week, and two cases could not be convinced that a substitution had been made. Stability was easily and effectively maintained by the substituted product so long as it was administered (12 to 17 days). Subsequent to abrupt and complete withdrawal of dilaudid, abstinence phenomena set in rather promptly, becoming marked–severe on the first day, severe on the second day, marked on the third, and thereafter followed by rapid recovery.

The ratio of equally effective doses of morphine to dilaudid is shown in table A. It would seem that the potency of dilaudid is approximately four times that of morphine. The group average morphine requirement in grams per man per day was 0.34; that of dilaudid was 0.09.

TABLE A.—*Ratio of effective doses*

Subject no.	Grams per day	
	Morphine	Dilaudid
1	0.4	0.1
2	.4	.08
3	.2	.06
4	.2	.06
5	.2	.06
6	.2	.06
7	.8	.2
Group average	.34	.09

An analysis of the data on defecation shown in table B would appear to indicate that in the same individuals under the same conditions, equally effective doses of morphine and dilaudid are equally constipating. The group averaged 1.3 bowel movements per man per day while on morphine and 1.24 while on dilaudid.

TABLE B.—*Average number of bowel movements per day*

Subject no.	Morphine	Dilaudid
1	1.2	1.8
2	1.3	1.9
3	1.3	.57
4	1.6	1.0
5	1.6	.85
6	.7	.9
7	1.3	[1] 1.5
Group average	1.3	[1] 1.24

[1] Abstinence diarrhea which occurred on the first day of dilaudid substitution is not included (case 7).

A similar analysis of hours of sleep on morphine versus dilaudid indicates no essential difference in this respect. While on morphine the group averaged 5.8 hours of sleep per man per day, and 6.04 hours while on dilaudid. The data are presented in table C.

TABLE C.—*Average number of hours of sleep per 24 hours*

Subject no.	Morphine	Dilaudid
1	5.6	4.85
2	6.2	5.2
3	6.5	5.85
4	5.1	6.2
5	5.6	6.2
6	8.6	8.7
7	4.6	5.54
Group average	5.8	6.04

COMMENT

At first the subjects were unaware of the substitution to dilaudid. Later they all noticed that the drug being administered was somewhat more powerful than morphine and that the duration of its effect was considerably (1 to 2 hours) shorter. None felt that the action of the substituted compound differed from that of morphine in any other way. Uneasiness and mild anxiety were observed 3 to 3½ hours after injections of dilaudid, which usually are noticeable 5 to 5½ hours after injections of morphine.

The syndrome of abstinence phenomena following withdrawal of dilaudid differed from that usually observed after morphine deprivation in that it set in more promptly and intensely and was of somewhat shorter duration. The total duration of intense abstinence manifestations was, however, about the same as observed following abrupt mor-

phine deprivation. During abstinence the subjects begged for some of the substituted product. The time of onset and degree of severity of abstinence symptoms are presented graphically and compared with unpublished data on abrupt morphine deprivation (fig. 1).

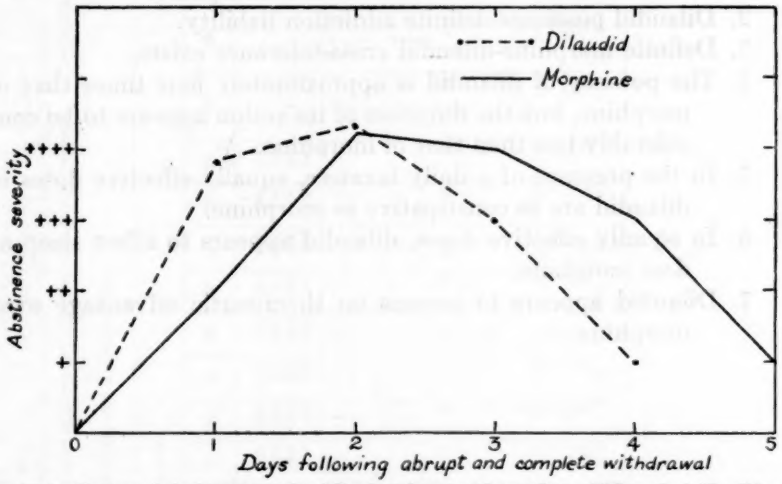

FIGURE 1.—Degrees of abstinence severity following abrupt and complete withdrawal of dilaudid and morphine.

One of the best indications of abstinence is the weight loss subsequent to withdrawal. The weight loss curves shown in figure 2 confirm the total abstinence curves shown in figure 1. The weight loss

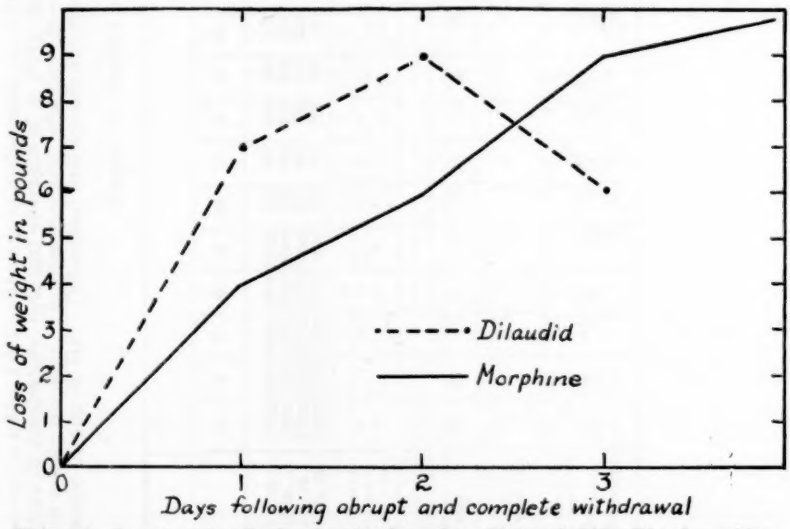

FIGURE 2.—Loss of weight following abrupt and complete withdrawal of dilaudid and morphine.

subsequent to dilaudid withdrawal is more rapid and shows earlier recovery than after abrupt morphine deprivation. The values shown for morphine abstinence are taken from unpublished data.

CONCLUSIONS

From observations made on morphine addicts, involving the substitution of dilaudid for morphine, it is concluded that—

1. Dilaudid is an effective substitute for morphine.
2. Dilaudid possesses definite addiction liability.
3. Definite morphine-dilaudid cross-tolerance exists.
4. The potency of dilaudid is approximately four times that of morphine, but the duration of its action appears to be considerably less than that of morphine.
5. In the presence of a daily laxative, equally effective doses of dilaudid are as constipative as morphine.
6. In equally effective doses, dilaudid appears to affect sleep as does morphine.
7. Dilaudid appears to possess no therapeutic advantage over morphine.

Notations for tables 1 to 7.—Dosage in milligrams. m = Morphine sulphate. d = Dihydromorphinone HCl. * = Presence of manifestation. Values of respiratory rate are averages of 3 daily determinations at 6 a. m., 12 m., and 5 p. m. D = dilated pupils. Appetite: P = poor; F = fair; 0 = none. Appearance and behavior: N = nervous; R = restless; W = weak. Weight is given in pounds; sleep in hours; blood pressure in mm of Hg. Defecation and emesis are reported in whole numbers covering the 24-hour period. P = paraldehyde.

TABLE 1.—*Subject no. 1: Dihydromorphinone substitution*

	July 1934																										
	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Doses: 6 a. m.	100m	100m	100m	100m	100m	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d					
12 m.	100m	100m	100m	100m	100m	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	30d	30d	30d	30d	30d					
5 p. m.	100m	100m	100m	100m	100m	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d					
10 p. m.	100m	100m	100m	100m	100m	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	30d	30d	30d	30d	30d	30d	30d					
Yawning				*						*	*			*			*		*				*	*	*	*	
Lacrimation	*		*	*		*	*	*				*	*				*		*				*					
Rhinorrhea	*			*	*	*										*							*	*	*	*	*
Perspiration						*																		*	*		
Goose flesh																								*			
Muscle tremor																							*	*	*	*	
Size of pupils																								D	D		
Respiration rate	26	24	23	21	17	18	25	22	21	23	22	22	19	20	17	25	21	21	23	24	22	24	24	25	24	21	28
Appetite																							P	0	0	P	F
Emesis																							1	2	2		
Defecation	2		1	1	2	1	2	2	1	4	3	1	2	2	1	2	2	1	1	2	2	2	4	2	2	2	2
Appearance and behavior																							N/R	N/R	W/R	W	W
Weight	147	144	141	140	141	140	140	141	140	141	141	140	140	142	141	140	140	140	140	141	142	140	142	134	132	133	135
Sleep	6½	6½	4	6½	5	5	5½	5	4½	5	5½	3½	4½	4	4	6	5	6½	4	3½	6	5	6	8P	8½P	5	6½
Blood pressure	152	124	112	134	112	118	120	130	134	116	134	128	120	106	116	130	114	122	126	114	118	124	122	120	128	114	116
	102	90	82	94	74	83	90	86	84	85	86	82	82	74	78	84	84	88	86	88	92	78	78	78	86	90	88
Degree of abstinence	+	0	0	+	0	+	0	0	0	0	0	0	0	0	0	0	+	0	+	0	0	0	++++	++++	++++	++	++

TABLE 2.—*Subject no. 2: Dihydromorphinone substitution*

	July 1934																							August 1934	
	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	1	2
Doses: 6 a. m.	100m	100m	100m	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d							
Doses: 12 m.		100m	100m	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d							
Doses: 5 p. m.		100m	100m	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d							
Doses: 10 p. m.		100m	100m	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d	20d							
Yawning							•					•	•	•			•	•	•	•	•	•		•	
Lacrimation				•						•	•								•	•	•	•		•	
Rhinorrhea											•								•	•	•	•	•	•	•
Perspiration																			•	•	•	•	•		
Goose flesh																			•	•	•	•	•	•	•
Muscle tremor																									
Size of pupils																				D					
Respiration rate		22	21	19	25	22	22	22	20	23	20	23	23	22	22	25	21	22	27	28	26	26	23	28	27
Appetite																			P	0	F	F			
Emesis																			1	5	3				
Defecation		2	2	2	2	3	2	2	3	2	1	1	1	2	2	1	2	2	4	3	5	6	5	3	3
Appearance and behavior																			N/R	N/R	N/R	W/R	W		
Weight	193	195	196	199	200	197	197	197	196	197	198	198	197	198	197	199	199	200	199	189	187	186	187	187	187
Sleep		4½	8	5½	4½	5	6	5½	5	4½	3½	6	6	6	5	6	4½	5	6	7P	4	4½	7P	4½	7
Blood pressure		122	120	114	130	118	132	126	110	110	110	100	110	100	98	110	98	110	116	132	132	124	126	118	120
		76	78	72	86	70	84	76	60	68	76	62	68	58	60	66	64	66	70	72	72	80	78	78	80
Degree of abstinence		0	0	0	0	0	0	0	0	0	+	0	0	0	0	0	0	0	++++	++++	++++	+++	++	++	++

TABLE 3.—*Subject no. 3: Dihydromorphinone substitution*

	July 1934															August 1934					
	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	1	2	3	4	5	6
Doses: 6 a. m.	50m	50m	50m	10d	10d	10d	10d	10d	10d	15d	15d	15d	15d	15d	15d	15d	15d				
Doses: 12 m.	50m	50m	50m	10d	10d	10d	10d	10d	15d	15d	15d	15d	15d	15d	15d	15d	15d				
Doses: 5 p. m.	50m	50m	50m	10d	10d	10d	10d	10d	15d	15d	15d	15d	15d	15d	15d	15d	15d				
Doses: 10 p. m.	50m	50m	50m	10d	10d	10d	10d	10d	15d	15d	15d	15d	15d	15d	15d	15d	15d				
Yawning	•						•		•		•		•				•	•	•	•	
Lacrimation				•	•	•	•		•	•								•	•		
Rhinorrhea									•										•		
Perspiration																		•	•	•	
Goose flesh																			•		
Muscle tremor				•	•																
Size of pupils																		D	D		
Respiration rate	17	14	12	13	15	15	15	17	15	17	17	16	17	15	16	18	14	16	15	17	18
Appetite																		P	F		
Emesis																			2		
Defecation	1	2	1			1	1	2	1				1		1		1	3	4	3	1
Appearance and behavior																		N/R	N/R		
Weight	149	145	142	143	145	147	150	148	147	150	150	149	148	147	147	145	143	143	141	141	144
Sleep	4	3	6	4	5	5	5½	5½	6	5	6	6½	6	6	6½	7½	7½	7	12	8½	8½
Blood pressure	132	128	130	130	126	118	114	112	118	118	110	114	114	114	118	120	112	120	116	108	110
	88	80	80	70	74	72	70	68	68	66	68	70	68	60	68	78	74	80	82	72	74
Degree of abstinence	0	0	0	+	+	0	+	0	+	0	0	0	0	0	0	0	0	++	++++	+	0

TABLE 4.—*Subject no. 4: Dihydromorphinone substitution*

	July 1934															August 1934					
	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	1	2	3	4	5	6
Doses: 6 a. m.	50m	50m	50m	10d	10d	10d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d				
12 m.	50m	50m	50m	10d	10d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d				
5 p. m.	50m	50m	50m	10d	10d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d				
10 p. m.	50m	50m	50m	10d	10d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d				
Yawning				•	•				•						•		•	•	•	•	•
Lacrimation						•											•	•	•	•	
Rhinorrhea									•									•	•		
Perspiration				•														•	•	•	
Goose flesh																					
Muscle tremor																		•	•		
Size of pupils																		D	D		
Respiration rate	16	17	18	19	20	19	19	18	21	21	20	19	18	19	17	16	16	21	19	23	22
Appetite																		P	P		
Emesis																			2		
Defecation	1	2	2	1	3	2	1	1	1		1	1	1	1	1			4	2	6	3
Appearance and behavior																		N/R	W/R	N/R	
Weight	132	131	131	132	131	132	130	130	130	133	132	130	131	130	129	129	127	130	124	122	123
Sleep	4½	5	6	4½	5½	7½	4½	5	5½	6½	7½	7	4½	8½	6½	8½	6	6½	12P	5½	6
Blood pressure	116	119	110	108	110	116	120	122	110	124	122	120	118	116	118	120	112	120	114	114	118
	78	72	70	64	66	66	76	66	60	70	74	62	76	66	64	68	78	72	70	82	74
Degree of abstinence	0	0	0	+	0	0	0	0	+	0	0	0	0	0	0	0	+	+++	++++	+++	+

TABLE 5.—*Subject no. 5: Dihydromorphinone substitution*

	July 1934															August 1934					
	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	1	2	3	4	5	6
Doses 6 a. m.	50m	50m	50m	10d	10d	10d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d				
Doses 12 m.	50m	50m	50m	10d	10d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d				
Doses 5 p. m.	50m	50m	50m	10d	10d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d				
Doses 10 p. m.	50m	50m	50m	10d	10d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d				
Yawning			•		•	•			•	•								•	•	•	•
Lacrimation									•		•							•	•	•	•
Rhinorrhea									•									•	•	•	
Perspiration				•														•	•		
Goose flesh																					
Muscle tremor								•										•	•		
Size of pupils																		D	D		
Respiration rate	18	18	20	20	19	18	21	19	22	19	19	23	19	18	17	20	22	21	33	31	29
Appetite																		P	P	F	
Emesis																		1			
Defecation	2	2	1	1		2	2		1		1		2	1	1		1	1	1	4	3
Appearance and behavior																		N/R	N/R	N/R	W
Weight	146	148	146	148	148	146	149	148	148	151	151	150	148	149	149	147	147	147	139	138	139
Sleep	6	5	6	6	5½	5½	4	6½	6	5½	6	6	7	7	5	9½	7½	7½	12P	5	6
Blood pressure	110	90	76	84	98	102	108	102	98	116	114	116	118	108	108	98	110	106	112	114	118
	60	62	42	50	62	66	62	68	62	50	74	72	64	70	80	62	80	78	84	80	88
Degree of abstinence	0	0	0	0	0	0	0	0	+	0	0	0	0	0	0	0	0	++++	++++	+++	+

TABLE 6.—*Subject no. 6: Dihydromorphinone substitution*

	July 1934		August 1934																			
	30	31	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Doses: 6 a. m.	50m	50m	50m	50m	10d	10d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	------	------	------	------	------
12 m.	50m	50m	50m	50m	10d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	------	------	------	------	------
5 p. m.	50m	50m	50m	50m	10d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	------	------	------	------	------
10 p. m.	50m	50m	50m	50m	10d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	15d	------	------	------	------	------
Yawning	------	------	------	------	------	------	------	------	------	------	------	------	------	------	•	------	------	•	•	•	•	------
Lacrimation	------	------	------	------	•	------	------	------	------	------	------	------	------	------	------	------	------	•	•	------	------	------
Rhinorrhea	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	•	------	------	------
Perspiration	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	•	------	------	------
Goose flesh	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	•	•	------	------	------
Muscle tremor	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	•	•	------	------	------
Size of pupils	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	D	D	D	D	D
Respiration rate	16	15	15	15	17	18	17	16	16	17	19	17	18	14	16	16	17	20	25	26	24	26
Appetite	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	F	F	------	------
Emesis	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	4	------	------	------
Defecation	------	1	------	2	1	------	1	------	1	3	1	1	1	------	1	------	2	4	10	7	4	1
Appearance and behavior	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	N/R	R	------	------
Weight	112	112	110	111	111	110	111	110	110	110	109	109	109	108	109	109	110	110	105	105	106	105
Sleep	8½	7½	9½	9	10½	8½	7½	7½	7½	8½	9½	10	9	8½	10½	6	11	12	6½	3	4	8
Blood pressure	128	124	120	114	108	106	125	110	120	112	108	122	116	112	102	100	106	110	116	116	118	120
	90	76	80	68	74	68	82	68	78	68	62	66	64	66	62	60	68	70	72	72	78	80
Degree of abstinence	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	++	++++	+++	++	0

TABLE 7.—*Subject no. 7: Dihydromorphinone substitution*

	August 1934																	
	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Doses: 6 a. m.	200m	200m	200m	40d	40d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d			
Doses: 12 m.	200m	200m	200m	40d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d			
Doses: 5 p. m.	200m	200m	200m	40d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d			
Doses: 10 p. m.	200m	200m	200m	40d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d	50d			
Yawning	•			•	•				•		•	•	•	•	•	•	•	•
Lacrimation		•		•	•	•					•	•	•	•		•	•	•
Rhinorrhea					•								•			•	•	•
Perspiration																	•	
Goose flesh																	•	•
Muscle tremor					•	•										•	•	•
Size of pupils																		
Respiration rate	15	13	18	19	18	14	16	18	16	18	18	17	17	14	16	17	21	23
Appetite					F	P	P									0	0	0
Emesis					2	5										10	23	16
Defecation	2	1	1	4	1	1		1	2	2	2	2	2	2	2	8		
Weight	199	198	200	199	198	195	193	193	195	196	197	196	195	196	195	195	184	180
Sleep	6½	4	3½	4	7	5½	7	4	4½	5½	8½	4½	6	4½	5½	5½	1	4½P
Appearance and behavior					N/R	N/R										N/R	N/R	W/R
Blood pressure	110	108	110	112	110	114	112	110	112	114	110	118	110	108	112	114	142	126
Blood pressure	76	74	80	72	78	76	72	78	74	72	78	80	78	80	74	74	82	84
Degree of abstinence	0	0	0	+	++++	++++	0	0	0	0	+	+	+	+	0	++++	++++	++++

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